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(74) Agent: BECKER, Konrad; Novartis AG, Patent– und Markenabteilung, Lichtstrasse 35, CH–4002 Basel (CH).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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(54) Title: ANTISENSE INHIBITION OF HUMAN STAT–6

(57) Abstract

An oligonucleotide having 10 to 30 nucleotide units which is complementary to at least part of mRNA encoding human Stat–6 and is capable of inhibiting expression of Stat–6.

ANTISENSE INHIBITION OF HUMAN STAT-6

This invention relates to oligonucleotides and to their use in pharmaceutical compositions.

Interleukin-4 (IL-4) is a cytokine protein which plays an important role in the induction of allergic-asthmatic immune responses. In vivo inhibition of IL-4 by neutralizing antibodies selectively prevents IgE antibody formation and TH2 cell generation - both significant factors in the induction and maintenance of the allergic-asthmatic response. IL-4 signalling is mediated by intra cellular proteins which act as signal transducers and activators of transcription (Stats). IL-4 induces Stat-6 protein activation, which is responsible for selective gene activation, for example in IgE production.

In accordance with the present invention, there have been prepared oligonucleotides which are capable of inhibiting expression of Stat-6 and may be used to inhibit the induction and maintenance of allergic-asthmatic reactions.

Accordingly, the present invention provides, in one aspect, oligonucleotides having 10 to 30 nucleotide units which are complementary to at least part of mRNA encoding human Stat-6 and are capable of inhibiting expression of Stat-6.

The oligonucleotides, which are believed tc function by an antisense mechanism, being specifically hybridisable with mRNA deriving from the Stat-6 gene, may have a base sequence, complementary to a base sequence in the coding region or the 5'- or 3'-untranslated region of the mRNA encoding human Stat-6, or in a region overlapping the 5'-untranslated region and the translation initiation site of this mRNA which preferably has a sequence corresponding to the published sequence of human Stat-6 cDNA or allelic variants thereof. The sequence of this cDNA is accessible in the GenBank ™/ EMBL Data Bank under Accession No. U16031. Preferably the oligonucleotides of the invention have a base sequence complementary to a part of the base sequence of mRNA encoding human Stat-6 ranging from base position 157(5') to 2874(3'), in particular from base position 157(5') to 2855(3'). More preferred oligonucleotides have a base sequence complementary to a part of the sequence of mRNA encoding human Stat-6 ranging from base position 1456(5') to 2573(3'), in particular from base position 1456(5') to 2554(3').

In oligonucleotides of the invention, there is preferably at least one phosphorothioate linkage, i.e. at least one of the internucleotide (backbone) linkages is a phosphorothioate linkage, the remaining internucleotide linkages being natural (phosphodiester) linkages or synthetic analogues thereof such as phosphorothioate or methyl phosphonate, or mixtures thereof.

In certain embodiments of the invention, the oligonucleotide preferably has at least one nucleotide unit modified at the 2' position, for example a nucleotide having at the 2' position an atom or group which enhances target binding affinity. In these embodiments, preferably at least one of the nucleotide units has at the 2' position a group of formula -OR where R is a C_1 to C_{10} aliphatic group, preferably a C_1 to C_{10} alkyl group optionally interrupted by one or more oxygen atoms, for example a C_1 to C_4 alkyl group such as methyl, ethyl, propyl or butyl, a C_1-C_4 alkoxy- C_1-C_4 alkyl group such as methoxyethyl or ethoxyethyl or a group of formula $-(CH_2CH_2O)_nCH_3$ or $-(CH_2CH_2O)_nCH_2CH_3$ where n is 2, 3 or 4, such as $(CH_2CH_2O)_3CH_3$. In especially preferred such embodiments, R is methxoyethyl, i.e. a group of formula $-CH_2CH_2OCH_3$.

In one preferred class of oligonucleotides according to the invention, all linkages between nucleotide units are phosphorothioate linkages. In this preferred class, most or all of the nucleotide units are preferably 2'-deoxynucleotides, i.e. they have sugar moieties as found in natural nucleic acids.

Another preferred class of oligonucleotides according to the invention have a first region which when bound to mRNA creates a substrate for RNAse H, in which region the linkages between nucleotide units are phosphorothioate linkages, between two outer regions in which the linkages between nucleotide units are phosphodiester linkages. In this class, the first region preferably has at least 4, more preferably at least 6 nucleotide units. In this first region, preferably all of the nucleotide units are 2'-deoxynucleotides. The outer regions preferably each have at least one nucleotide, more preferably 50 to 100% of the nucleotides thereof, modified at the 2' position as hereinbefore described, more preferably having at the 2' position a group of formula -OR where R is a C_1 to C_{10} aliphatic group, preferably a C_1 to C_{10} alkyl group optionally interrupted by one or more oxygen atoms, especially a group of formula $-CH_2CH_2OCH_3$.

oligonucleotide no. 16 of the Examples), an oligonucleotide having the base sequence of SEQ ID NO 8 and the specific structure 5'-TCCCC$_s$C$_s$A$_s$G$_s$T$_s$G$_s$A$_s$G$_s$C$_s$G$_s$AATGGA-3' (i.e. oligonucleotide no. 18 of the Examples), an oligonucleotide having the base sequence of SEQ ID NO 9 and the structure 5'-GTGAG$_s$G$_s$T$_s$C$_s$C$_s$T$_s$G$_s$T$_s$T$_s$C$_s$AGTGGG-3' (i.e. oligonucleotide no. 19 of the Examples), an oligonucleoitde having the base sequence of SEQ ID NO 1 and the specific structure of 5'-CCCCA$_s$C$_s$A$_s$G$_s$A$_s$G$_s$A$_s$C$_s$A$_s$T$_s$GATCTG-3' (i.e. oligonucleotide no. 20 of the Examples), an oligonucleotide having the base sequence of SEQ ID NO 4 and the specific structure of 5'-CGGTC$_s$C$_s$A$_s$T$_s$C$_s$T$_s$C$_s$A$_s$G$_s$A $_s$GAAGGC-3' (i.e. oligonucleotide no. 23 of the Examples), an oligonucleotide having the base sequence of SEQ ID NO 6 and the specific structure 5'-CTCCG$_s$G$_s$A$_s$G$_s$A$_s$C$_s$A$_s$G$_s$C$_s$G$_s$TTTGGT-3' (i.e. oligonucleotide no. 25 of the Examples), an oligonucleotide having the base sequence of SEQ ID NO 8 and the specific structure 5'-TCCCC$_s$C$_s$A$_s$G$_s$T$_s$G$_s$A$_s$G$_s$C$_s$G$_s$AATGGA-3' (i.e. oligonucleotide no. 27 of the Examples), and an oligonucleotide having the base sequence of SEQ ID NO 9 and the specific structure 5'-GTGAG$_s$G$_s$T$_s$C$_s$C$_s$T$_s$G$_s$T$_s$T$_s$C$_s$AGTGGG-3' (i.e. oligonucleotide no. 28 of the Examples), wherein each of "A", "T", "C" or "G" denotes the respective 2'-deoxynucleotide building block, each of "A", "T", "C" or "G" denotes the respective 2'-methoxyethoxy-modified 2'-deoxynucleotide building block, each suffix "$_s$" denotes a phosphorothioate internucleoside linkage, and no specific indication at a location of an internucleoside linkage denotes a phosphodiester linkage.

Within the context of the present invention the term "oligonucleotide" may encompass a salt or mixed salt of an oligonucleotide, where salt-forming groups are present, in particular a pharmaceuticaly tolerated salt, i.e. essentially a non-toxic salt. For example, a suitable salt may be a lithium salt, a sodium salt, a magnesium salt, a zinc salt or a potassium salt, with a sodium salt being preferred.

Oligonucleotides of the invention may be conveniently prepared using well-known techniques such as solid phase synthesis based, for example, on coupling reactions involving nucleotides having a 3' phosphoramidite or 3' H-phosphonate group and a protected 5' hydroxyl group and nucleotides having a free 5' hydroxyl group. Equipment for such synthesis is available commercially from various sources including Applied Biosystems. The use of such techniques to prepare oligonucleotides having phosphorothioate linkages and 2'-modifications such as those hereinbefore described is well-known.

= Mitogen activating protein kinase, OptiMEM = opti-minimal essential medium, reduced serum medium, PBS = phosphate buffered saline, PVDF = Polyvinylidene fluoride, SDS-PAGE = sodium dodecyl sulphate poly acrylamide gel electrophoresis, Stat-6 = Signal Transducer and Activator of Transcription-6, T = Thymidine.

Examples 1-10

Oligonucleotides having phosphorothioate internucleotide linkages are prepared by conventional solid phase synthesis, on controlled pore glass (CPG) using phosphoramidite chemistry and tetraethylthiuram disulphide as sulphurising agent. They have the following sequences, "s" denoting a phosphorothioate internucleotide linkage (the corresponding SEQ ID NOs of the respective base sequences are likewise shown)

Oligonucleotide No. / SEQ ID NO	Sequence (5' - 3' - direction)
1 / SEQ ID NO 1	$C_sC_sC_sC_sA_sC_sA_sG_sA_sG_sA_sC_sA_sT_sG_sA_sT_sC_sT_sG$
2 / SEQ ID NO 2	$C_sT_sT_sT_sC_sA_sC_sA_sC_sC_sT_sC_s\ T_sC_sC_sT_sG_sG_sA_sG$
3 / SEQ ID NO 3	$T_sC_sA_sG_sA_sG_sA_sA_sG_sG_sC_s\ A_sT_sT_sG_sT_sC_sC_sC_sA$
4 / SEQ ID NO 4	$C_sG_sG_sT_sC_sC_sA_sT_sC_sT_sC_sA_sG_sA_sG_sA_sA_sG_sG_sC$
5 / SEQ ID NO 5	$T_sT_sT_sC_sA_sC_sA_sC_sA_sT_sC_sT_sT_sC_sT_sC_sC_sC_sA_sG$
6 / SEQ ID NO 6	$C_sT_sC_sC_sG_sG_sA_sG_sA_sC_sA_sG_sC_sG_sT_sT_sT_sG_sG_sT$
7 / SEQ ID NO 7	$C_sT_sG_sG_sA_sT_sG_sT_sT_sC_sT_sC_sT_sA_sT_sC_sT_sG_sT_sG$
8 / SEQ ID NO 8	$T_sC_sC_sC_sC_sC_sA_sG_sT_sG_sA_sG_sC_sG_sA_sA_sT_sG_sG_sA$
9 / SEQ ID NO 9	$G_sT_sG_sA_sG_sG_sT_sC_sC_sT_sG_sT_sT_sC_sA_sG_sT_sG_sG_sG$
10 / SEQ ID NO 10	$C_sC_sA_sC_sT_sG_sT_sG_sC_sA_sT_sT_sC_sT_sC_sC_sT_sG_sT_sT$

Oligonucleotides Nos. 2 to 9 are complementary to sequences in the coding region of human Stat-6 mRNA, while Oligonucleotide No. 1 is complementary to a sequence overlapping the 5' untranslated region and the translation initiation site and Oligonucleotide No. 10 is complementary to a sequence in the 3' untranslated region of human Stat-6 mRNA.

Oligonucleotides Nos. 12 to 19 and 21 to 28 are complementary to sequences in the coding region of human Stat-6 mRNA, while Oligonucleotides Nos. 11 and 20 are complementary to a sequence overlapping the 5' untranslated region and the translation initiation site.

Example 29

The activity of Oligonucleotides 1 to 28 is tested in human lung A 549 cells. Lipofectin® - mediated transfection of oligonucleotides into A 549 cells is used for in vitro activity testing. A 549 cells are cultured in DMEM (Gibco-BRL, cat# 41965-039) containing 15% FBS (Gibco-BRL, cat# 10106-151) to approximately 75% confluency in six-well plates. Prior to transfection, cells are washed in PBS to remove culture-medium. OptiMEM + Lipofectin® is added to each well (1 ml per well), followed by addition of the oligonucleotide. For optimal transfection efficiencies, 3 µl Lipofectin® is mixed with 1 ml OpiMEM (Gibco-BRL, cat# 31985-47) when using 100 nM of oligonucleotide (e.g. 400 nM oligonucleotide = 12 µl Lipofectin in 1 ml OptiMEM). The cells are incubated at 37°C for 4 hours, after which the transfection-medium is replaced with normal culture-medium.

Cells are treated twice (0h and 24h) with 500 nM of the oligonucleotide and are harvested after 48 hours. Harvested cells are lysed then boiled in 300 µl protein loading-buffer and 30 µl are loaded onto a 10% SDS-PAGE gel. Gel separation is performed at 100 V for 1 hour. The separated proteins are then transferred onto a PVDF membrane from Millipore (cat# P15552). Stat-6 is detected using the polyclonal Stat-6 antibody (1:1000; Santa Cruz, sc-981) and the ECF detection kit (Amersham, UK; RPN-5780). The membranes are scanned using the PhosphorImager (Molecular Dynamics) using the chemifluorescence detection mode. Protein levels are quantitated using Quantanalysis software (Molecular Dynamics) and normalised by reference to Mapk (Erk 2). The results are shown below.

Oligonucleotide No.	% Reduction of Stat-6 Protein Level
1	61
2	15
3	30

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: NOVARTIS AG

(B) STREET: Schwarzwaldallee 215

(C) CITY: Basel

(E) COUNTRY: Switzerland

(F) POSTAL CODE: 4058

(G) TELEPHONE: +41 61 324 1111

(H) TELEFAX: +41 61 322 75 32

(ii) TITLE OF INVENTION: Organic compounds

(iii) NUMBER OF SEQUENCES: 10

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy Disk

(B) COMPUTER: IBM PC Compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: Word 6.0

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

CCCCACAGAG ACATGATCTG (20)

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

CGGTCCATCT CAGAGAAGGC (20)

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

TTTCACACAT CTTCTCCCAG (20)

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

GTGAGGTCCT GTTCAGTGGG (20)

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

CCACTGTGCA TTCTCCTGTT (20)

11. An oligonucleotide according to claim 10, in which at least one of the nucleotide units has at the 2' position a group of formula -OR where R is a C_1 to C_{10} aliphatic group.

12. An oligonucleotide according to claim 11, in which R is a C_1 to C_{10} alkyl group optionally interrupted by one or more oxygen atoms.

13. An oligonucleotide according to claim 12, in which R is a group of formula $-CH_2CH_2OCH_3$.

14. An oligonucleotide according to any of the preceding claims, in which all linkages between nucleotide units are phosphorothioate linkages.

15. An oligonucleotide according to any of claims 1 to 13 having a first region which when bound to mRNA creates a substrate for RNAse H in which linkages between nucleotide units are phosphorothioate linkages between outer regions in which linkages between nucleotide units are phosphodiester linkages.

16. An oligonucleotide according to claim 15, in which said first region has at least 4 nucleotide units.

17. An oligonucleotide according to claim 15 or 16, in which in said first region all of the nucleotide units are 2'-deoxynucleotides.

18. An oligonucleotide according to claim 15, 16 or 17, in which the outer regions each have at least one nucleotide modified at the 2' position.

19. An oligonucleotide according to claim 18, in which the outer regions each have 50 to 100% of the nucleotides thereof modified at the 2' position.

20. An oligonucleotide according to claim 18 or 19, in which at least one of the modified nucleotides has at the 2' position a group of formula -OR where R is a C_1 to C_{10} aliphatic group.

5'-TCCCC$_s$C$_s$A$_s$G$_s$T$_s$G$_s$A$_s$G$_s$C$_s$G$_s$AATGGA-3', an oligonucleotide having the base sequence of SEQ ID NO 9 and the structure 5'-GTGAG$_s$G$_s$T$_s$C$_s$C$_s$T$_s$G$_s$T$_s$T$_s$C$_s$AGTGGG-3', an oligonucleotide having the base sequence of SEQ ID NO 1 and the specific structure of 5'-CCCCA$_s$C$_s$A$_s$G$_s$A$_s$G$_s$A$_s$C$_s$A$_s$T$_s$GATCTG-3', an oligonucleotide having the base sequence of SEQ ID NO 4 and the specific structure of 5'-CGGTC$_s$C$_s$A$_s$T$_s$C$_s$T$_s$C$_s$A$_s$G$_s$A $_s$GAAGGC-3', an oligonucleotide having the base sequence of SEQ ID NO 6 and the specific structure 5'-CTCCG$_s$G$_s$A$_s$G$_s$A$_s$C$_s$A$_s$G$_s$C$_s$G$_s$TTTGGT-3', an oligonucleotide having the base sequence of SEQ ID NO 8 and the specific structure 5'-TCCCC$_s$C$_s$A$_s$G$_s$T$_s$G$_s$A$_s$G$_s$C$_s$G$_s$AATGGA-3', and an oligonucleotide having the base sequence of SEQ ID NO 9 and the specific structure 5'-GTGAG$_s$G$_s$T$_s$C$_s$C$_s$T$_s$G$_s$T$_s$T$_s$C$_s$AGTGGG-3', wherein each of "A", "T", "C" or "G" structures denotes the respective 2'-deoxynucleotide building block, each of "A", "T", "C" or "G" denotes the respective 2'-methoxyethoxy-modified 2'-deoxynucleotide building block, each suffix "$_s$" denotes a phosphorothioate internucleoside linkage, and no specific indication of an internucleoside linkage denotes a phosphodiester linkage.

28. A pharmaceutical composition comprising as active ingredient an oligonucleotide according to any one of the preceding claims optionally together with a pharmaceutically acceptable carrier.

29. The use of an oligonucleotide according to any one of claims 1 to 27 in the preparation of a medicament for the treatment of a disease modulated by Stat-6.

30. The use of an oligonucleotide according to any one of claims 1 to 27 in the preparation of a medicament for the treatment of asthma.

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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: NICKLIN, Paul, Leslie [GB/GB]; Tanglewood, West End Lane, Henfield, West Sussex BN5 9RE (GB). HILL, Sandra, Jane [GB/GB]; 4 Haybarn Drive, Horsham, West Sussex RH12 5JF (GB). PHILLIPS, Judith, Ann [GB/GB]; 46 Lyndhust Drive, Sevenoaks, Kent TN13 2HQ (GB). HERLAAR, Helena, Catharina [NL/GB]; 24 Garden Place, Hawthorn Close, Horsham, West Sussex RH12 2BD (GB). GRAHAM, Brent [US/GB]; 42 High Street, Burwell, Cambridge CB5 0HD (GB).

(74) Agent: BECKER, Konrad; Novartis AG, Patent– und Markenabteilung, Lichtstrasse 35, CH–4002 Basel (CH).

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(54) Title: ANTISENSE INHIBITION OF HUMAN STAT–6

(57) Abstract

An oligonucleotide having 10 to 30 nucleotide units which is complementary to at least part of mRNA encoding human Stat–6 and is capable of inhibiting expression of Stat–6.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/11 C07H21/04 A61K31/70

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 02023 A (SMITHKLINE BEECHAM CORP :DUNNINGTON DAMIEN JOHN (US)) 23 January 1997 see claims ---	29,30
A	ALTMANN K H ET AL: "SECOND-GENERATION ANTISENSE OLIGONUCLEOTIDES: STRUCTURE-ACTIVITY RELATIONSHIPS AND THE DESIGN OF IMPROVED SIGNAL-TRANSDUCTION INHIBITORS" BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 24, no. 3, August 1996, pages 630-637, XP000671118 see the whole document ---	9-24,27

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
3 September 1998	21/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Andres, S

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INTERNATIONAL SEARCH REPORT

.nformation on patent family members

Intc ional Application No
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